REMARKS

This Reply is responsive to the Office Action dated May 19, 2004. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested in light of the Request for Continued Examination filed concurrently herewith.

I. Amendments to the Claims

Claims 10 and 15 have been amended. Claim 10 as amended specifies that the method takes place in the presence of appropriate assay components and under conditions effective to detect inhibition of the transfer of a phosphorous molecule from ATP to phosphomevalonate. Support for this amendment may be found in the specification, for example at page 11, line 10 through page 12, line 2. Claim 15 as amended specifies that the polypeptide to which the antibody component of the claim binds, exhibits at least one of the same antigenic determinants as the protein of SEQ ID NO:7. Support for this amendment may be found in the specification, for example at page 14, lines 17-21 with respect to the discussion of selective binding.

Claims 16 – 24 have been added and are drawn to distinct embodiments of the same invention claimed in claim 1. Claims 16 and 18 specify that the polypeptide is naturally occurring in a species of *Candida albicans*. Support for these claims may be found in the specification, for example at page 4, lines 5-12 and page 6, lines 6-9. Claim 17 specifies that the polypeptide results from the expression of a nucleic acid that hybridizes under stringent conditions to SEQ ID No.:6, which encodes the protein of SEQ ID No.:7. Support for this claim may be found at least at page 4, line 24 through page 6, line 3. Claims 19-23 specify alternative % identity of the polypeptides claimed with respect to SEQ ID No.:7. Support for these claims may be found for example at page 4, lines 13-17. Claim 24 specifies that the polypeptide is that of SEQ ID No.:7. Support for this claim is found in original claim 1 and throughout the specification.

No prohibited new matter has been added by way of these amendments.

II. Rejection under 35 U.S.C. §112, First Paragraph

Claims 1, 10 and 15 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being admittedly enabling for an isolated and purified polypeptide comprising the amino acid sequence, SEQ ID No. 7, a method to identify compounds that inhibit PMK activity of *C. albicans* by contacting a test compound with the polypeptide SEQ ID No. 7, and a diagnostic kit comprising antibodies that bind to SEQ ID No. 7, allegedly fails to enable polypeptides possessing at least 90% similarity to SEQ ID No. 7 and the use of such polypeptides in the manner claimed. According to the Office Action, while recombinant and mutagenesis techniques are known, it is allegedly not routine in the art to screen for multiple modifications of polypeptides with a reasonable expectation of success in obtaining similar activity. Applicants respectfully traverse the rejection, particularly in light of the declaration of Dr. John Rosamond.

First, Applicants again respectfully note that independent claim 1 is drawn to polypeptides having phosphomevalonate kinase (PMK) activity comprising the amino acid sequence depicted in SEQ ID No. 7 or a sequence possessing at least 90% identity thereto. Accordingly, the invention includes only functional variants having a sequence that is at least 90% identical to SEQ ID No. 7. Variants that retain PMK function as now claimed would certainly be useful in diagnostic kits to identify compounds that inhibit PMK activity.

Further, while the Examiner may be correct that mutation of a single amino acid may eliminate antigen recognition by a single antibody, it is equally true that most proteins can accommodate numerous mutations while still retaining function and antibody binding. This is evident from the fact that many proteins exist in different allelic forms in nature and there are numerous publications of functional mutant forms of proteins that include substitution mutations, truncations, and additions (including fusion proteins). The state of the art at the filing date of the invention was such that it was well within the capabilities of a person skilled in the art to perform targeted or random

mutagenesis on a protein sequence and test the activity or the immunogenicity of the mutant proteins.

For instance, as noted above, the specification discloses that nucleotide changes or mutations may be introduced into a polynucleotide sequence by *de novo* polynucleotide synthesis, by site directed mutagenesis using appropriately designed oligonucleotide primers or by any other convenient means known in the art (page 8, lines 12-15).

With respect to the question of what part of the polypeptide could be altered while maintaining PMK activity, the declaration of John Rosamond clearly describes how one skilled in the art would undertake such a selection of regions capable of modification without loss of the essential functionality. As stated by the declarant "a person skilled in the art would be able to use one of several algorithms to align the ERG8 protein sequences from *Candida albicans* (hereinafter C. albicans) and *Saccharomyces cerevisiae* (hereinafter S. cerevisiae) based on information available prior to the filing dates associated with this application. One example of such an alignment is shown in Figure 1. From such an alignment, the person skilled in the art would be able to identify regions of contiguous sequence that are conserved in both proteins, as exemplified by the regions of the proteins shown in bold italicized text in Figure 1. The conservation of such regions or domains would be known by this person as likely to play a key role in the enzymatic activity of the protein, for example by making key contributions to the 3-dimensional structure of the active site. Consequently, a person skilled in the art would recognize that these regions were unlikely to be able to accommodate changes to the amino acid sequence."

The declarant continues further stating the "from the same alignment, a person skilled in the art would recognize regions that showed less overall conservation as being those parts of the protein that could potentially accommodate mutation without loss of biological function. On the basis of published data comparing other functional homologs

from C. albicans and S. cerevisiae, (for example Sherlock et al., (1994) Molecular & General Genetics 245, 716-723; Nolan & Rosamond, (1996) Gene 183, 159-165) it would be known to a person skilled in the that such regions are typically found at the N- and C-termini of the proteins. Analysis of the aligned ERG8 proteins (Figure 1) reveals that these proteins have relatively little identity beyond residue 385 of the C. albicans protein. This region would be seen to provide scope for deletion or a series of point mutations that would be likely to retain biological function."

The means of producing such modified proteins are well known to the skilled artisan. As Dr. Rosamond further states, "using the cognate DNA sequence for the ERG8 gene, the person skilled in the art would be able to design primers that could be used to amplify the ERG8 gene by PCR. The primers could be further designed to modify a specific amino-acid residue in the C-terminal region or to engineer the deletion of the residues downstream of amino acid 385. The amplified product would be ligated into a suitable plasmid vector, which would be cloned, then transformed into a strain of bacterium to express the product of the ERG8 gene. Function of the mutated ERG8 gene on the plasmid would be assessed by the ability to generate active phosphomevalonate kinase using any one of several well known assays for detecting the change in ATP and ADP levels that represent the activity of PMK in the presence of phospohmevalonate."

The issue of whether experimentation is undue cannot be assessed in the absence of a consideration of the nature of the involved technology, the skill level of the artisans and the type of experimentation that would be routine. As noted in *In re Wands* 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the analysis of undue experimentation must consider what is routine for the practitioner in the art as an acceptable level of further inquiry not a point of undue breadth.

In addition to the discussion above about what one of ordinary skill in the art could readily undertake to identify regions of the polypeptide that would be available for alteration by design without loss of function, the invention includes naturally occurring variants of the specific ERG8 protein set forth in SEQ ID No.: 7 in which the alterations

are naturally occurring. The specification clearly contemplates and describes such naturally occurring variants. See for example page 4, lines 5-12 and page 6, lines 6-9.

The skilled artisan would anticipate the presence of such allelic variant proteins and would be able to isolated them without undue experimentation. As John Rosamond states the identification of such variants would be routine for the skilled artisan. Note paragraph 6 of the declaration wherein he states "In addition to a gross deletion of a region of the ERG8 protein, as described above, a person skilled in the art would recognize that strains carrying multiple point mutations in the ERG8 gene could be identified rapidly either occurring naturally in clinical isolates of C. albicans as a result of natural allelic polymorphism or engineered after random mutagenesis."

Dr. Rosamond continues stating that "a person skilled in the art would know that significant natural allelic variation occurs in all characterized microbial pathogens, including C. albicans (for example Miyazaki et al. (1999) Gene 236, 43-51). These natural variants contain single or multiple amino-acid changes in proteins when compared with the original reference strain, although the proteins retain biological activity as evidenced by the viability of the clinical isolates. Recognizing this, a person skilled in the art would be able to clone the ERG8 gene from any collection of clinical isolates of C. albicans using well established methods followed by the use of standard methods to determine the sequence of any one of the naturally occurring ERG8 genes, and hence the naturally occurring C. albicans ERG 8 proteins, from each clinical isolate. Comparing this sequence with the reference sequence shown in Figure 1 would rapidly identify natural variants of the ERG8 protein that, per se, will retain enzymatic activity."

Given that the application clearly describes how to make and screen for naturally occurring functional variants, the application certainly teaches one of skill in the art how

to make functional variants in a manner reasonably correlated with the scope of the amended claims.

The Office action comments that the specification provides "essentially no guidance as to which screening assay for PMK activity is likely to be successful." The Office action does not provide any factual evidence to the effect that one skilled in the art would require such guidance, nor that there is any factual basis for doubting that each of the described assays will be successful in identifying those polypeptides that meet the claimed requirement that the polypeptide possesses PMK activity.

The specification describes numerous ways to screen for PMK activity, including the use of assays that measure increase in ADP production, assays that measure loss of ATP, and assays that monitor the transfer of a radioactive label into phosphomevalonate (page 11, line 10, to page 12, line 2). Each of these assays is well known to the skilled artisan and does not raise any issues with respect to undue experimentation in the application of these well-known assays.

In addition to naturally occurring allelic variants the induction of random mutations in a genome are well known techniques and do not require undue experimentation on the part of the skilled artisan. As Dr. Rosamond states in this regard, "a person skilled in the art would be aware that PCR is itself mutagenic and could be used rapidly to generate multiple random variants of the C. albicans gene that could be screened for enzymatic activity. For this, such a person would design primers that would anneal to regions upstream and downstream of the ERG8 gene. These primers would be used to amplify the ERG8 gene by PCR using conditions know to favor error-prone amplification (for example Vartanian J.P. et al. (1996) Nucleic Acids Research 24, 2627-2631). The products of the amplification would be cloned into a plasmid vector such that the gene product would be expressed in a bacterium and the activity of the resultant protein assayed using one of the methods described in the application. This would allow the rapid identification of variants of the ERG8 protein that retain enzymatic activity but which might vary from the sequence shown in Figure 1 by one or several residues."

Thus, a skilled artisan possesses the knowledge and tools necessary to make and to identify embodiments of the invention distinct from SEQ ID No.: 7 without engaging in undue experimentation, especially those that vary from the specific sequence by no more than 10%. Limiting the claims to a specific embodiment of the invention in light of the inclusion of its specific amino acid sequence in the specification is unwarranted and unduly restrictive. The information in the specification coupled with the routine skill and knowledge of the ordinary artisan affords the skilled artisan with the capacity to make and use many additional embodiments of the invention. The fact that experimentation may be complex does not make it undue. Correct application of the factors articulated in *In re Wands, supra* together with the information in the specification and the skill and knowledge of the artisan necessitates a conclusion that the current claims are not unduly broad. The routine nature of the work required to make embodiments other than the polypeptide of SEQ ID No.:7 is confirmed by the statements of Dr. John Rosamond who is not only himself a skilled artisan but whom is very familiar with the skill and knowledge of one who routinely endeavors in this area of technology, and the publications cited by Dr. Rosamond. The examiner's attention is respectfully directed to the discussion of pertinent case law as presented in Section 2164.01 of the M.P.E.P.

In view of the amendments and remarks above, reconsideration and withdrawal of the rejection of under §112, first paragraph for lack of enablement is respectfully requested.

This reply is fully responsive to the Office Action dated May 19, 2004. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, he or she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully Submitted,

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